## Introduction:

Along with Industrialization and globalization, many new diseases are arising in the world, infections caused by the microorganisms render a major contribution to it. Some of the infections are acute and some are chronic which may be air born, water born or food born. Unhygienic conditions are determined to be the root cause for these infections. In addition to it, the development of resistance in microorganisms against current antimicrobial therapy continues to drive the search for more effective antimicrobial drugs [1].

Antimicrobial drugs are the greatest contribution of the 20$^{th}$ century to therapeutics as their advent changed the outlook of physicians about the power drugs. Their importance is magnified in the developing countries, where infective diseases predominate. Drugs in this class differ from all others in that they are designed to inhibit/kill the infecting organism and to have no/minimal effect on the recipient. Such type of therapy is generally called "*chemotherapy"*. The basis of selective microbial toxicity is the action of drug on a component of the microbe (e.g. bacterial cell wall) or metabolic process (e.g. Folate synthesis) that is not found in the host, or high affinity for certain microbial bio-molecules (e.g. trimethoprim for bacterial dihydrofolate reductase). Due to analogy between the malignant cell and the pathogenic microbes, treatment of neoplastic diseases with drugs is also called '*chemotherapy*' [2].

Since microorganisms develop rapid resistance, there is an ample scope for the development of new antimicrobial agents that are active against resistant microorganism. There is a great need to synthesize the compounds, which are capable of treating both acute and chronic infections.

In order to combat the microbial infections, antimicrobial drugs are frequently used concurrently i.e. the combined use of antimicrobial with following objectives,

- To prevent emergence of resistance.
- To lower the adverse or side effects.
- To have a synergetic effect.
- To broaden the anti-microbial spectrum.

Metal complex of heterocyclic compounds are of challenging interest in therapeutic chemistry, and this has catalyzed the innovation and development of much new heterocyclic chemistry and methods. It is equally interesting for its theoretical implication for the diversity of its synthetic procedure and for the physiological and industrial significances. Synthetic heterocyclic drugs are used as hypnotics, anticonvulsants, antiseptics, antineoplastics, antiviral, antihistaminic, antitumor etc. Majority of the drugs being introduced in pharmacopeias every year are heterocyclic compounds. Sulphar and nitrogen containing heterocyclic compounds and their fused analogs represent an important class of drugs in the therapeutic chemistry and also contributed to the society from biological and industrial point which helps to understand life processes. [3] They exist in numerous natural products, [4] displaying wide range of biological and pharmaceutical activities. [5-7].

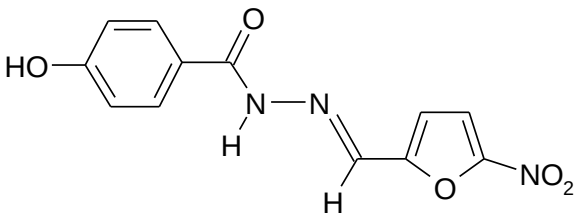
Complexing agents are becoming of increasing importance in drug chemistry, new types of complexing agents are constantly under investigation, for possible analytical and industrial applications. The growing importance of the use of metal chelates in drug chemistry may be realized by the ever-increasing number of publications on this subject.

The formation of Chelate and its stability depends upon the following three aspects.

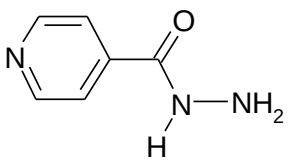
- The central metal atom
- The Chelate forming groups of molecules
- The nature of the metal-ligand bond

Earlier studies of complexing agents were aimed at long term preparative work and modifications of reagent structures, experimental evaluation of their reactivity, selectivity and properties of the Complex species formed with the analyte. More recently modern structural methods together with theoretical and empirical numerical approaches have become important, especially for radiation absorbing reagents and their reaction products. The expected properties can then be interpreted using models of atomic and electronic structure. Such work contributes to a better knowledge and understanding of complexing agents so that the selectivity and reactivity of each new complexing agent may be predicted. The formation of binary, ternary or quaternary Chelate species may also lead to the establishment of complex equillibria which must be elucidated. In general, the main aim in preparing a new Complexing agent, or in optimizing the reactivity of a known reagent, is to increase sensitivity, selectivity or method reliability for an analyte.

Hydrazones have been known to possess, antimicrobial, anticonvulsant, analgesic, anti-inflammatory, antiplatelet, antitubercular and antitumor activities.

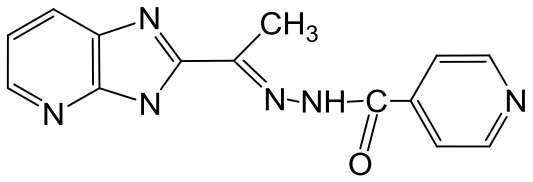



Nifuroxazide



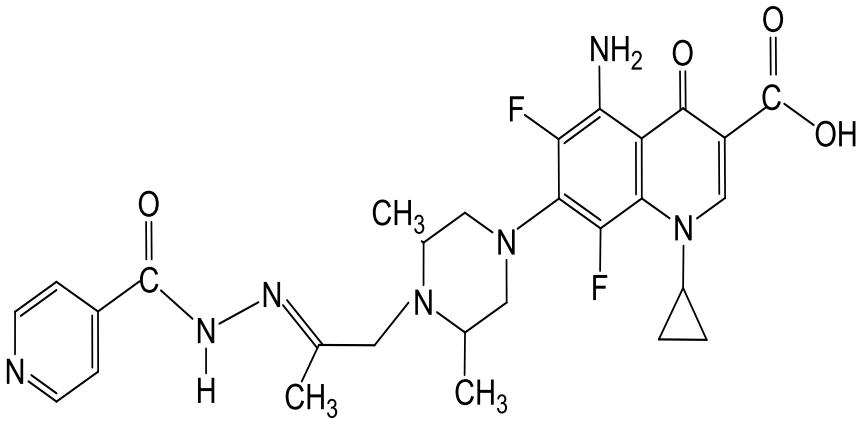

Isoniazid

The reaction of 2-acetylimidazo [4,5-b] pyridine with isoniazide yielded the corresponding hydrazidehydrazones. This compound exhibited activity against *M. tuberculosis*. *M. tuberculosis*, isolated from patients and resistant against isoniazide, ethambutol, rifampicine at 3.13 µg/ml [8].



(*E*)-*N*'-(1-(3*H*-imidazo[4,5-*b*]pyridin-2-yl)ethylidene)isonicotinohydrazide

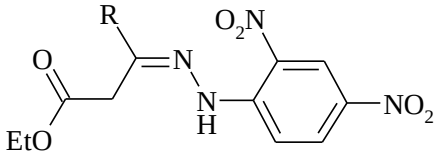
Novel fluoroquinolones containing a hydrazone structure were synthesized and evaluated in vivo against M. tuberculosis in Swiss albino mice by Shindikar et al, Results of the study indicate the potent antitubercular activity of the test compounds [9].



formaldehyde compound with 5-amino-1-cyclopropyl-6,8-difluoro-3,7-dimethylquinolin-4(1*H*)-one and methanol and 2,6-dimethylpiperazine and 2-methylbut-1-ene and 4-methylpyridine and methane and methylhydrazine (2:1:1:1:1:1:1:1)

It is seen that very limited work has been reported on derivatives of Oxo Butyric acid ester till date.

Sarbani Pal, Jyoti Mareddy and Nalla Suneeta devi [10] reported high speed synthesis of pyrazolones using microwave assisted neat reaction technology. This greener synthetic methodology involves the reaction of β-keto ester with substituted or unsubstituted hydrazine and provides a simple and straightforward one-pot approach for the synthesis of a variety of pyrazolone derivatives with high regioselectivity.

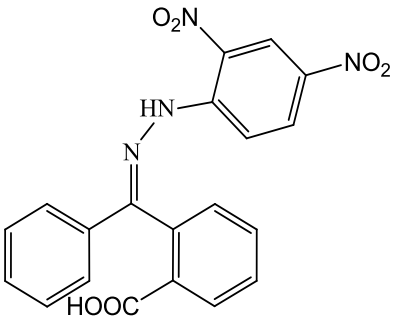



R = $CH_3$, $C_6H_5$

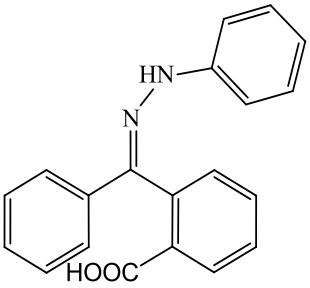
R= -CH3, (Z)-ethyl 3-(2-(2,4-dinitrophenyl)hydrazono)butanoate

R= -C6H5, (E)-ethyl 3-(2-(2,4-dinitrophenyl)hydrazono)-3-phenylpropanoate

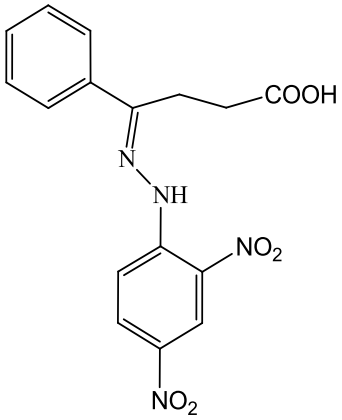
Z. M. Gadhawala, M. K. Modasiya and R. M. Doi [11] reported synthesis and biological evaluation of some new oxime, phenyl hydrazone and 2,4-di nitro phenyl hydrazone derivatives of ketone. Various oximes, phenylhydrazones and 2, 4 dinitrophenylhydrazones have been synthesized by reaction with different ketonic compounds. The structures of these compounds have been confirmed on the basis of spectral data. The antimicrobial activity of the prepared compounds is discussed and some of them are found to be active.



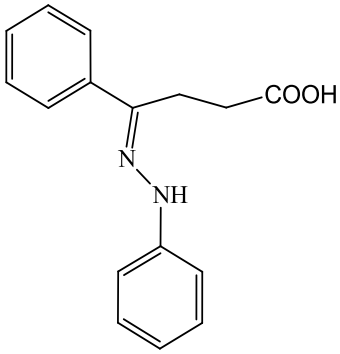

(*Z*)-2-((2-(2,4-dinitrophenyl)hydrazono)(phenyl)methyl)benzoic acid




(*Z*)-2-(phenyl(2-phenylhydrazono)methyl)benzoic acid

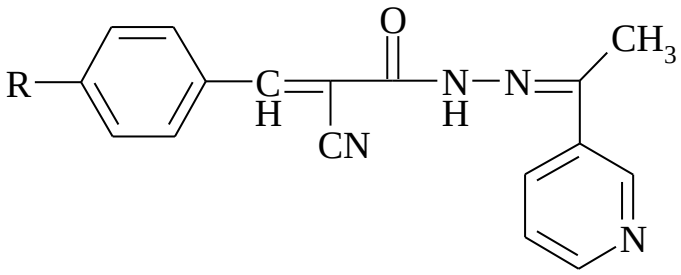



(*E*)-4-(2-(2,4-dinitrophenyl)hydrazono)-4-phenylbutanoic acid




(*E*)-4-phenyl-4-(2-phenylhydrazono)butanoic acid

Rafat M. Mohareb, Daisy H. Fleita and Ola K. Sakka [12] synthesised hydrazide – hydrazone derivatives and studied their utilization in the synthesis of coumarin, pyridine, thiazole and thiophene derivatives with antitumor activity.

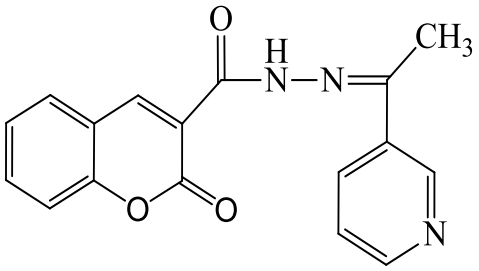



R = H, Cl, $OCH_3$

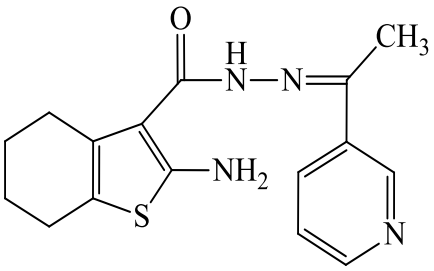
R=H, 3-phenyl-2-cyano-N'-(1-(pyridin-3-yl)ethylidene)acrylohydrazide

R=-Cl, 3-(4-chlorophenyl)-2-cyano-N'-(1-(pyridin-3-yl)ethylidene)acrylohydrazide

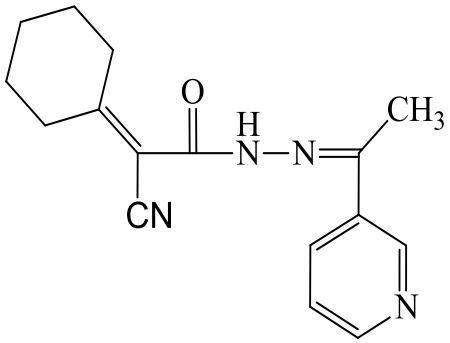
R= - $OCH_3$, 3-(4-methoxyphenyl)-2-cyano-N'-(1-(pyridin-3- yl)ethylidene)acrylohydrazide



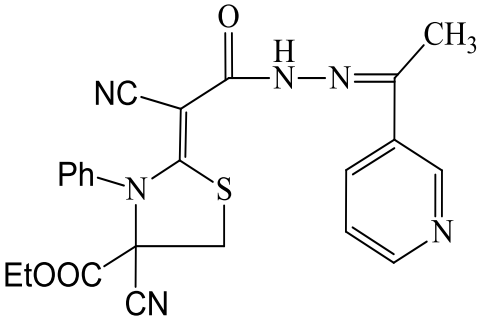
2-oxo-*N*'-(1-(pyridin-3-yl)ethylidene)-2*H*-chromene-3-carbohydrazide



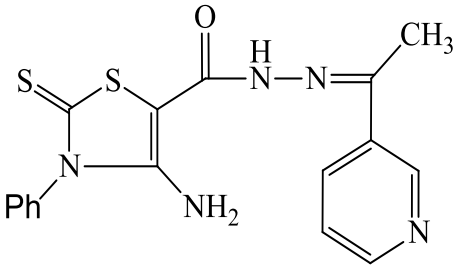
2-amino-*N*'-(1-(pyridin-3-yl)ethylidene)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbohydrazide



2-cyano-2-cyclohexylidene-*N*'-(1-(pyridin-3-yl)ethylidene)acetohydrazide

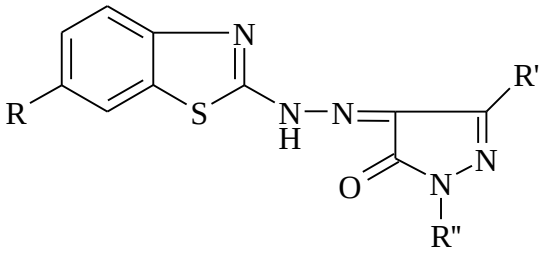


(2*Z*)-ethyl 4-cyano-2-(1-cyano-2-oxo-2-(2-(1-(pyridin-3-yl)ethylidene)hydrazinyl)ethylidene)-3-phenylthiazolidine-4-carboxylate



4-amino-3-phenyl-*N*'-(1-(pyridin-3-yl)ethylidene)-2-thioxo-2,3-dihydrothiazole-5-carbohydrazide

V. Khatri, K. Sharma, V. Sareen and D. Shindhe [13] reported synthesis, characterization and biocidal activity of novel halogenated-4-[(substituted-benzothiazol-2-yl)hydrazono]-2-(substituted-phenyl)-5-methyl/ethoxy-2,4-di hydro-pyrazol-3-one derivatives.




R= -X , R' & R"= -H, 4-(2-(6-halogenobenzo[d]thiazol-2-yl)hydrazono)-1H-pyrazol-5(4H)-one

R"= -ph , R & R'= -H, 4-(2-(benzo[d]thiazol-2-yl)hydrazono)-1-phenyl-1H-pyrazol-5(4H)-one

R'= -Me, R & R"= -H, 4-(2-(benzo[d]thiazol-2-yl)hydrazono)-3-methyl-1H-pyrazol-5(4H)-one

R'= -OEt ,R & R"= -H, 4-(2-(benzo[d]thiazol-2-yl)hydrazono)-3-ethoxy-1H-pyrazol-5(4H)-one

## Objectives:

The brief and latest review about hydrazide derivatives and Oxy butyric acid ester derivatives has been reviewed and it was noted that the reaction of various aceto acetate derivatives with aromatic hydrazine derivatives has not been reported. Hence, substituted phenyl hydrazono butanoate derivatives have been thought to prepare for metal chelating study. Thus, the objective of the Ph.D. work is to synthesis, characterize and study the chelating properties of substituted phenyl hydrazono butanoate derivatives [L-1 to L-12].

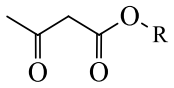
## The present work:

According to the objectives the Ph.D research work was carried out and the work will be bifurcated into following chapters of the proposed thesis.

**Chapter -1** will include,

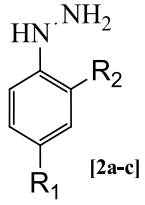
- Introduction
- Review about chelating agents
- Brief note on hydrazone derivatives
- Brief note on Oxo butyric acid ester derivatives
- Objective and present work

The condensation reaction between various aceto acetate derivatives and hydrazide derivatives was carried out. The resultant substituted phenyl hydrazono butanoate derivatives [L-1 to L-12] were isolated. The details about the synthesis procedure of these compounds will be presented in **Chapter- 2**.



[1a-d]

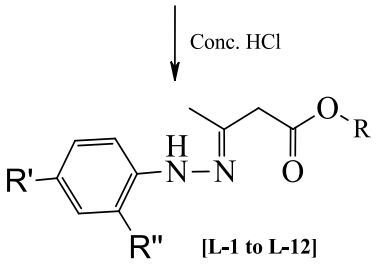
+



[2a-c]

1a (R= -$CH_3$) methyloxobutanoate
1b (R= -$C_2H_5$) ethyloxobutanoate
1c (R= -$CH_2$-$C_6H_5$) benzyloxobutanoate
1d (R= -$CH(CH_3)_2$) isopropyloxobutanoate

2a ($R_1$,$R_2$= -H) phenyl hydrazine
2b ($R_1$,$R_2$= -$NO_2$) 2,4-dinitro phenyl hydrazine
2c ($R_1$= -$NO_2$, $R_2$= -H) 4-nitro phenyl hydrazine

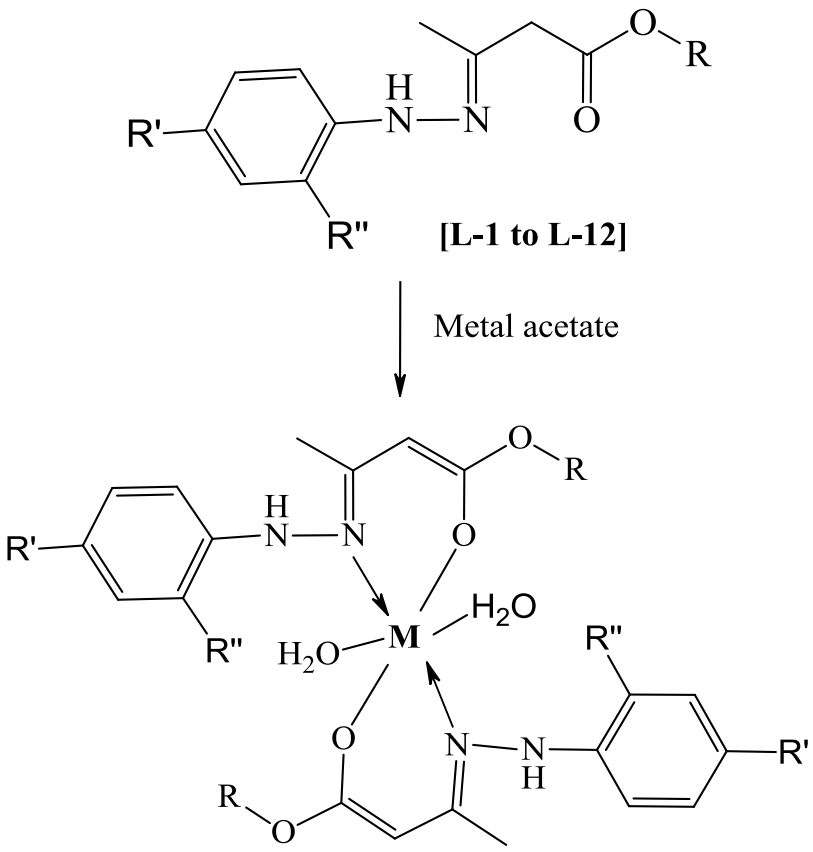



[L-1 to L-12]

$l_1$ (R= -CH3, R1&R2= -H) methyl 3-(2-phenylhydrazono)butanoate
$l_2$ (R= -CH3, R1&R2= -NO2) methyl 3-(2-(2,4-dinitrophenyl)hydrazono)butanoate
$l_3$ (R= -CH3, R1= -NO2 & R2= -H) methyl 3-(2-(2,4-dinitrophenyl)hydrazono)butanoate
$l_4$ (R= -C2H5, R1&R2= -H) ethyl 3-(2-phenylhydrazono)butanoate
$l_5$ (R= -C2H5, R1&R2= -NO2) ethyl 3-(2-(2,4-dinitrophenyl)hydrazono)butanoate
$l_6$ (R= -C2H5, R1= -NO2 & R2= -H) ethyl 3-(2-(2,4-dinitrophenyl)hydrazono)butanoate
$l_7$ (R= -CH2-C6H5, R1&R2= -H) benzyl 3-(2-phenylhydrazono)butanoate
$l_8$ (R= -CH2-C6H5, R1&R2= -NO2) benzyl 3-(2-(2,4-dinitrophenyl)hydrazono)butanoate
$l_9$ (R= -CH2-C6H5, R1= -NO2 & R2= -H) benzyl 3-(2-(2,4-dinitro phenyl) hydrazono) butanoate
$l_{10}$ (R= -CH(CH3)2, R1&R2= -H) isopropyl 3-(2-phenylhydrazono)butanoate
$l_{11}$ (R= -CH(CH3)2, R1&R2= -NO2) isopropyl 3-(2-(2,4-dinitrophenyl)hydrazono)butanoate
$l_{12}$ (R= -CH(CH3)2, R1= -NO2 & R2= -H) isopropyl 3-(2-(2,4 dinitrophenyl) hydrazono) butanoate

The compounds mentioned in chapter-2 are designated as ligands and characterized by elemental analysis and IR, NMR, MS spectral features. All these will be included in **chapter-3**.

The various transition metal ($Cu^{+2}$, $Co^{+2}$, $Mn^{+2}$, $Ni^{+2}$, $Zn^{+2}$) complexes of all the novel ligands $L_1$ to $L_{12}$ were prepared and characterized primarily. The methods for metal chelates preparation and metal: ligand (M : L) stoichiometry will be presented in **chapter – 4**.

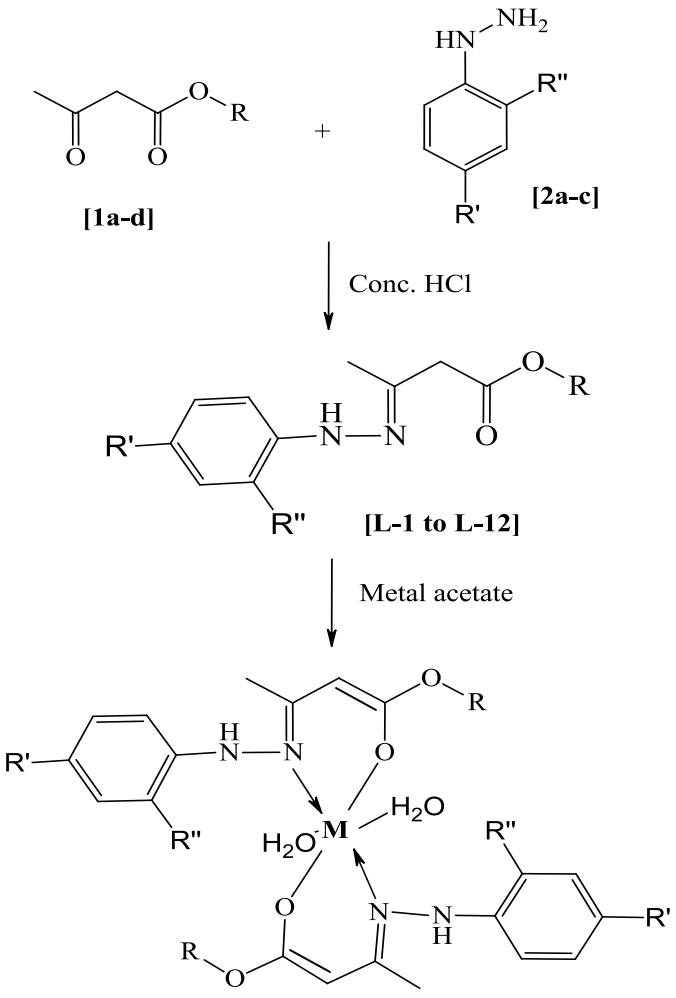



**Metal Chelates**

The general properties like Infrared spectral studies, magnetic measurements and electronic spectral scanning of all the chelates have been carried out. The results of $\mu_{eff}$ and transition states of the chelates of all the derivatives mentioned in chapter-2 were interpreted and will be outlined in **chapter-5.** Here, Dye indicator method also performed to check composition of metal complexes and the data will be presented in chapter-5 of the thesis.

The **chapter -6** will comprises the evaluation of antimicrobial activity of all the ligands and their metal chelates. The various plant pathogens have been selected for this study.

The whole research work is summarized in **scheme – 1**




**Metal Chelates of $L_1$ to $L_{12}$**

Where, R = $-CH_3$, $-C_2H_5$ , $-CH_2C_6H_5$ , $-CH(CH_3)_2$

R', R" = H; R',R" = $NO_2$; R' = $NO_2$ and R" = H

M = $Cu^{+2}$ , $Ni^{+2}$ ,$Mn^{+2}$ , $Co^{+2}$ ,$Zn^{+2}$

**Scheme-1**

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[13] Khatri, V., Sharma, K., Sareen, V. and Shindhe, D., Heteroletters, Vol. 2(2), 174 (2012).

Signature of the
Supervising Teacher

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(Dr. Sunil I. Marjadi)
Campus Director,
Shree Nutan Kelavani Mandal,
Valsad

Signature of the
Student

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(Ushma V. Joshi)